

**FOOD AND DRUG
LABORATORIES, INC.**



MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378

FINAL

July 19, 1973

Teratologic Evaluation of FDA 71-47

(Lactose)

in

Rabbits

E17

Final report-Teratologic Evaluation of FD.. 71-47 (Lactose) in Rabbits
7/19/73

E17

RABBITS



FOOD AND DRUG
Research LABORATORIES, INC.
F I N A L
R E P O R T

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Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 19, 1973

Laboratory No. 1363 d
Contract No. FDA 71-260

Sample: Fine white powdered material

Marking: FDA 71-47 (Lactose)

Examination Requested: Teratologic evaluation of FDA 71-47 in rabbits

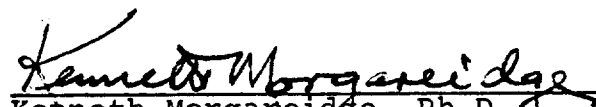
Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 1600 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

It is therefore concluded that lactose is not a teratogen for the rabbit.


Kenneth Morgareidge, Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 181 & 182; 187 through 190

Table 1

Date: June 18, 1973

Material: FDA 71-47

Fate Summary
(Rabbits)

Laboratory No. : 1363 d

Group	Material	Dose** mg/kg	Total		Surviving at Term	
			Mated	Pregnant	Total	Pregnant ¹
181	Sham	0.0	20	15	15	10
182	6-AN*	2.5	17	13	15	11
187	FDA 71-47	16.0	20	15	18	13
188	FDA 71-47	74.0	22	17	17	12
189	FDA 71-47	345.0	24	18	17	13
190	FDA 71-47	1600.0	27	20	18	12

* Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

** Administered as a water solution (See Appendix I)

¹) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 181 & 182; 187 through 190

Table 2

Date: June 18, 1973

Material: FDA 71-47

Reproduction Data
(Rabbits)

Laboratory No.: 1363 d

Group:	181	182	187	188	189	190
Dose (mg/kg):	Sham	6-AN**	16.0	74.0	345.0	1600.0
Pregnancies						
Total No.	15	13	15	17	18	20
Died or Aborted (before Day 29)	5	2	2	5	5	8
To term (on Day 29)	10	11	13	12	13	12
Corpora Lutea						
Total No.	216	166	198	226	312	347
Average/dam mated	10.8	9.76	9.90	10.3	13.0	12.9
Live Litters						
Total No.*	8	8	12	10	12	11
Implant Sites						
Total No.	62	54	75	80	85	76
Average/dam*	6.20	4.91	5.77	6.67	6.54	6.33
Resorptions						
Total No.*	9	12	5	24	12	11
Dams with 1 or more sites resorbed	5	8	5	7	3	4
Dams with all sites resorbed	1	3	--	2	1	--
Per cent partial resorptions	50.0	72.7	38.5	58.3	23.1	33.3
Per cent complete resorptions	10.0	27.3	--	16.7	7.69	--
Live Fetuses						
Total No.	47	41	66	56	73	59
Average/dam*	4.70	3.73	5.08	4.67	5.62	4.92
Sex ratio (M/F)	1.35	1.16	0.74	1.15	0.74	1.04
Dead Fetuses						
Total No.*	6	1	4	--	--	6
Dams with 1 or more dead	1	1	2	--	--	2
Dams with all dead	1	--	1	--	--	1
Per cent partial dead	10.0	9.09	15.4	--	--	16.7
Per cent all dead	10.0	--	7.69	--	--	8.33
Average Fetus Weight, g	37.2	33.5	41.2	39.9	40.2	33.4

* Includes only those dams examined at term.

** Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 181 & 182; 187 through 190

Laboratory No. 1363 d

Table 3

Material FDA 71-47

Date June 18, 1973

Summary of Skeletal Findings*
(Rabbits)

Findings	Group No. : Dose (mg/kg) :	181 Sham	182 6-AN**	187 16.0	188 74.0	189 345.0	190 1600.0
Live Fetuses Examined (at term)		32/7 ^a	40/8	67/12	56/10	69/11 ^a	51/10 ^a
Sternebrae							
Incomplete oss.			6/2	6/4		8/2	3/2
Scrambled							
Bipartite				1/1			
Fused			10/5		1/1		
Extra		2/2	1/1	2/2			
Missing			1/1	1/1		3/1	3/2
Other							
Ribs							
Incomplete oss.							
Fused/split			13/6				
Wavy							
Less than 12							
More than 13							
Other							
Vertebrae							
Incomplete oss.							
Scrambled			16/6				1/1
Fused							
Extra ctrs. oss.							
Scoliosis			13/6				1/1
Tail defects		1/1	35/8				1/1
Other							
Skull							
Incomplete closure			1/1				
Missing							
Craniosclerosis							2/1
Other							
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							

* Numerator=Number of fetuses affected; Denominator=Number of litters

** Positive control : 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9 affected.

^a One litter lost in processing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 181 & 182; 187 through 190

Date June 18, 1973

Material FDA 71-47

Table 3-a

Laboratory No. 1363 d

Summary of Soft Tissue Abnormalities
(Rabbits)

Group	Material	Dose Level mg/kg	Dam	Number of Pups	Description
182	6-AN*	2.5	Z 3272	3	Anopia; medial rotation of hind limbs
			Z 3275	4	Anopia
			Z 3276	5	Anopia; medial rotation of hind limbs

* Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 181 & 182; 187 through 190

Date June 18, 1973

Species Rabbits

Table 4

Laboratory No. 1363 d

Average Body Weights

Group	Material	Dose Level	-----Day-----				
			0	6	12	18	29**
mg/kg			-----g-----				
181	Sham	0.0	2.03	2.09	2.07	2.17	2.28 (10)
182	6-AN***	2.5	2.06	2.30	2.33	2.42	2.50 (11)
187	FDA 71-47	16.0	2.34	2.42	2.45	2.53	2.64 (13)
188	FDA 71-47	74.0	2.20	2.24	2.28	2.28	2.45 (12)
189	FDA 71-47	345.0	2.50	2.52	2.56	2.63	2.76 (13)
190	FDA 71-47	1600.0	2.23	2.28	2.29	2.33	2.44 (12)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9



Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

<u>Dosage</u> (mg/kg)	<u>Dose</u> (ml/kg)	<u>Concentration</u> (mg/ml)
≤ 250	1	≤ 250
251 - 500	2	125 - 250
501 - 750	3	133 - 250
751 - 1000	4	187 - 250
1001 - 1250	5	200 - 250
1251 - 1500	6	208 - 250
1501 - 1600	6.4	235 - 250

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.



On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 181
Material Sham
Dose 0.0 mg/kg

Appendix II

Date May 30, 1973
Laboratory No. 1363

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 3271	P	13	2	2		--	--		----	Aborted Day 22
S 3272	P	14	3	1		0	1	2	46.3	
S 3273	P	13	2					2	----	
S 3274	P	17	8	7		4	3	1	37.7	One Neonatal Death
S 3275	NP	1	0						----	
S 3276	P	12	5	2		1	1	3	43.3	
S 3277	NP	2	0						----	
S 3278	NP	0	0						----	
S 3279	P	9	4	--		--	--		----	Aborted Day 27
S 3280	P	7	3	--		--	--		----	Aborted Day 19
S 3281	P	22	4	4		--	--		----	Sacrificed Day 18
S 3282	NP	7	0						----	
S 3283	P	13	8	8		4	4		33.8	
S 3284	P	12	8	8		4	4		25.5	
S 3285	P	13	8	8		5	3		34.0	
S 3286	P	14	5	5		2	3		41.5	
S 3287	P	13	6		6				----	
S 3288	P	14	6	5		--	--	1	----	Died Day 13
S 3289	NP	5	0						----	
S 3290	P	15	9	8		7	1	1	35.7	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 182

Material 6-AN

Dose 2.5 mg/kg

Appendix II

Date May 30, 1973

Laboratory No. 1363

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
Z 3271	P	7	1					1	----	
Z 3272	P	16	3	3		1	2		29.7	Three Neonatal Deaths
Z 3273	P	7	2	--		--	--		----	Aborted Day 22
Z 3274	P	7	3					3	----	
Z 3275	P	20	5	4		3	1	1	38.8	One Neonatal Death
Z 3276	P	18	7	5		2	3	2	29.0	Four Neonatal Deaths
Z 3277	NP	5	0						----	
Z 3278	NP	8	0						----	
Z 3279	NP	11	0						----	
Z 3280	P	11	3	2		--	--	1	----	Died Day 21
Z 3281	P	11	4	3	1	2	1		46.1	
Z 3282	NP	8	0						----	
Z 3283	P	4	1					1	----	
Z 3284	P	---**	8	8		4	4		33.2	Eight Neonatal Deaths
Z 3285	P	12	9	8		4	4	1	30.3	Four Neonatal Deaths
Z 3286	P	10	6	5		3	2	1	28.2	Five Neonatal Deaths
Z 3287										Not Assigned
Z 3288	P	11	7	5		3	2	2	32.9	Two Neonatal Deaths

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 187

Material FDA 71-47

Dose 16.0 mg/kg

Appendix II

Date May 30, 1973

Laboratory No. 1363 d

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
D 3001	NP	10	0						----	
D 3002	P	10	7	7		2	5		38.0	
D 3003	P	9	7	6	1	2	4		46.0	
D 3004	P	15	6	5		3	2	1	46.3	
D 3005	P	14	5	3		--	--	2	----	Aborted Day 20
D 3006	P	8	6	6		2	4		49.1	
D 3007	NP	2	0						----	
D 3008	NP	1	0						----	
D 3009	NP	17	0						----	
D 3010	NP	2	0						----	
D 3011	P	15	7	6		2	4	1	35.6	One Neonatal Death
D 3012	P	11	7	6		2	4	1	34.3	
D 3013	P	10	3	3		1	2		42.3	
D 3014	P	---**	3		3				----	
D 3015	P	12	5	5		3	2		38.2	
D 3016	P	13	6	--		--	--		----	Died Day 28
D 3017	P	12	5	5		3	2		44.0	
D 3018	P	14	9	9		5	4		40.9	
D 3019	P	11	5	4		2	2	1	40.1	
D 3020	P	12	5	4		1	3	1	39.8	

* P = Pregnant; NP = Not Pregnant

** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 188

Appendix II

Date May 30, 1973

Material FDA 71-47

Laboratory No. 1363 d

Dose 74.0 mg/kg

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
D 3021	P	13	7	5		--	--	2	----	Sacrificed Day 27
D 3022	P	15	8	6		3	3	2	31.9	Three Neonatal Deaths
D 3023	P	29	8	8		--	--		----	Died Day 19
D 3024	P	8	7					7	----	
D 3025	P	15	5	5		--	--		----	Aborted Day 20
D 3026	NP	8	0						----	
D 3027	P	11	3	2		--	--	1	----	Died Day 26
D 3028	NP	1	0						----	
D 3029	P	7	6	6		2	4		34.4	
D 3030	P	7	5	--		--	--		----	Aborted Day 23
D 3031	P	10	9	9		6	3		38.5	
D 3032	P	10	5	4		2	2	1	41.1	
D 3033	NP	1	0						----	
D 3034	P	10	3	3		1	2		44.4	
D 3035	P	13	8					8	----	
D 3036	NP	9	0						----	
D 3037	P	15	8	7		3	4	1	40.7	
D 3038	P	9	8	7		3	4	1	38.6	
D 3039	NP	0	0						----	
D 3040	P	13	7	7		4	3		36.4	
D 3089	P	8	5	5		4	1		44.3	
D 3090	P	14	6	2		2	0	4	48.2	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 189

Appendix II

Date May 30, 1973

Material FDA 71-47

Laboratory No. 1363 d

Dose 345.0 mg/kg

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
D 3041	P	18	2	2		1	1		44.6	
D 3042	P	7	5	5		3	2		37.8	
D 3043	NP	0	0						----	Died Day 8
D 3044	NP	0	0						----	
D 3045	P	17	3	--		--	--		----	Sacrificed Day 12
D 3046	NP	2	0						----	
D 3047	NP	2	0						----	
D 3048	NP	7	0						----	
D 3049	P	27	9	6		--	--	3	----	Died Day 12
D 3050	P	9	4	4		--	--		----	Died Day 24
D 3051	NP	8	0						----	Died Day 18
D 3052	P	25	10	10		--	--		----	Died Day 6
D 3053	P	13	5	5		3	2		43.8	
D 3054	P	15	9	7		4	3	2	38.0	
D 3055	P	12	8	8		3	5		35.5	
D 3056	P	25	9	9		3	6		40.6	
D 3057	P	12	9	9		5	4		33.4	
D 3058	P	28	5	5		1	4		50.7	
D 3059	P	12	4	4		1	3		41.7	
D 3060	P	14	8	7		3	4	1	39.5	
D 3085	P	21	3	--		--	--		----	Died Day 8
D 3086	P	12	4	4		0	4		44.2	
D 3087	P	13	8	8		4	4		32.8	
D 3088	P	13	9					9	----	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 190

Appendix II

Date May 30, 1973

Material FDA 71-47

Laboratory No. 1363 d

Dose 1600.0 mg/kg

Reproduction Data in Rabbits (Individual)

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
D 3061	NP	5	0						----	
D 3062	P	13	3	2		--	--	1	----	Died Day 16
D 3063	NP	0	0						----	
D 3064	P	13	2					2	----	Died Day 18
D 3065	P	10	7	7		4	3		31.9	
D 3066	P	13	6	6		--	--		----	Sacrificed Day 10
D 3067	P	7	1	1		--	--		----	Died Day 11
D 3068	NP	1	0						----	
D 3069	NP	20	0						----	
D 3070	P	4	4	4		2	2		33.1	One Neonatal Death
D 3071	NP	4	0						----	
D 3072	NP	6	0						----	Died Day 8
D 3073	NP	11	0						----	
D 3074	P	18	7	7		--	--		----	Aborted Day 24
D 3075	P	11	5		5				----	
D 3076	P	16	2	1	1	0	1		41.1	One Neonatal Death
D 3077	P	12	7	7		3	4		41.4	
D 3078	P	10	8	8		--	--		----	Died Day 8
D 3079	P	19	7	7		--	--		----	Died Day 20
D 3080	P	10	4	4		2	2		35.4	
D 3081	P	13	6	4		1	3	2	20.9	Four Neonatal Deaths
D 3082	P	15	4	4		2	2		40.3	
D 3083	P	38	12	8		6	2	4	27.5	
D 3084	P	24	11	11		6	5		37.2	
D 3091	P	16	9	8		---**	---**	1	13.7	Eight Neonatal Deaths
D 3092	P	23	6	--		--	--		----	Died Day 10
D 3093	P	15	5	1		0	1	4	44.5	

* P = Pregnant; NP = Not Pregnant

** Not Recorded